The Metastatic Microenvironment: Local Activation of Endothelial Cells Promotes Tissue Colonization

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Abbreviations

ADP	Adenosine diphosphate
BDNF	Brain-derived neurotrophic factor
BMDC	Bone marrow-derived cells
CA	Carbohydrate antigen (CA125, CA19.9)
CAF	Cancer associated fibroblast
cDNA	Complementary deoxyribonucleic acid
CD	Cluster of differentiation
CI-MPR	Cation-independent mannose phosphate receptor
COX	Cyclooxygenase
CRC	Colorectal cancer
CSC	Cancer stem cell
CSF	Colony stimulating factor
CTC	Circulating tumor cell
cRNA	Complementary ribonucleic acid
DAPI	4’,6-diamidino-2-phenylindol
DNA	Deoxyribonucleic acid
DTC	Disseminated tumor cell
ECA	Endothelial cell activation
ECM	Extracellular matrix
EGF	Epithelial growth factor
EMT	Epithelial to mesenchymal transition
EPC	Endothelial progenitor cell
EpCAM	Epithelial cell adhesion molecule (CD326)
ERK	Extracellular signal-regulated kinase
ESL-1	E-selectin ligand 1
FACS	Flow activated cell sorting
FCS	Fetal calf serum
GAG	Glycosaminoglycan
Gal	Galactose
GalNAc	N-acetylgalactosamine
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GFP	Green fluorescent protein

GlcNAc	N-acetylglucosamine
GlcUA	Glucuronic acid
GRP78	Glucose regulated protein 78
HA	Hyaluronic acid
HGF	Hepatocyte growth factor
HIF	Hypoxia inducible factor
HMVEC	Human microvascular endothelial cells
HUVEC	Human umbilical cord endothelial cells
IGF	Insulin-like growth factor
IgG	Immunoglobulin G
IKK	Inhibitor of κ B kinase
IL	Interleukin
INF	Interferon
ISH	*In situ* hybridization
K14-HPV16 mouse	Transgenic mouse expressing the early region of human papilloma virus type 16 under the promoter of keratin 14 (Arbeit et al., 1994)
MAPK	Mitogen activated protein kinase
MMP	Matrix metalloprotease
NFκB	Nuclear factor κ B
NK cell	Natural killer cell
ORF	Open reading frame
OSGPase	O-sialoglyco-endoprotease
PAI-1	Plasminogen activator inhibitor 1
PAF	Platelet activating factor (acetyl-glyceryl-ether-phosphorylcholine
PAR	Protease activated receptor
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate buffered saline
PDGF	Platelet-derived growth factor
PGE2	Prostaglandin E 2
PIPES	Piperazine-N-N'-bis(2-ethanesulfonic acid)
PKC	Protein kinase C
PMN	Polymorphonuclear cells (neutrophil granulocytes)

PSGL-1	P-selectin glycoprotein ligand 1 (CD162)
RANKL	Receptor activator for NFκB ligand
RANTES	Regulated on activation, normal T-cell expressed and secreted
RBC	Red blood cells
RGS	Regulator of G-protein signaling
RIP-Tag mouse	Transgenic mouse expressing the large T antigen of the simian virus 40 under the rat insulin promoter (Hanahan, 1985)
RNA	Ribonucleic acid
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RT-PCR	Real time polymerase chain reaction
sLe^x	Sialyl-Lewis x
sLe^a	Sialyl-Lewis a
TAM	Tumor associated monocytes
TAN	Tumor associated neutrophils
TF	Tissue factor
TF-antigen	Thomsen-Friedenreich antigen (T-antigen, β1-3-Gal-GalNAcα-Ser/Thr)
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloproteases
TNF	Tumor necrosis factor
uPA	Urokinase-type plasminogen activator
VCAM-1	Vascular cell adhesion molecule (CD106)
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Summary

Metastasis remains the primary cause for the high morbidity and lethality of cancer. Dissemination of tumor cells via blood circulation is the main route for distant metastasis formation and leads to the colonization as well as the subsequent impairment of vital organs. Interactions of tumor cells with their microenvironment enhance their survival within the circulation and the successful colonization of distant tissues. In this study, we describe the cell-cell interactions of tumor cells with platelets, innate leukocytes and microvascular endothelial cells during early time points of tissue colonization. Selectins, vascular cell adhesion molecules, mediated interactions that induced an activation of the microvascular endothelium characterized by the upregulation of inflammatory proteins including the chemokine CCL5. Endothelial CCL5 led to a recruitment of circulating monocytes and facilitated the metastatic colonization. Monocytes enhanced tumor cell survival by supporting extravasation at distant sites. Furthermore, CCL5 concentrations were increased in the peripheral blood of colorectal cancer patients with metastasis when compared to patients with local disease or healthy controls. Collectively, these findings provide evidence that endothelial CCL5 is involved in the pathogenesis of metastasis and its inhibition could be a valid anti-metastatic approach.

Zusammenfassung

Die Entstehung von Tochtergeschwülsten, sogenannten Metastasen, ist der Hauptgrund für die hohe Sterblichkeit von Krebspatienten. Metastasen bilden sich, wenn Krebszellen in die Blutgefässe eindringen und über den Kreislauf zu Organen wie der Leber oder dem Gehirn transportiert werden. Im Kreislauf und im Gewebe solcher Organe kommt es zu Wechselwirkungen zwischen Tumorzellen, Blutzellen und Zellen der Gefässwände. In dieser Arbeit haben wir diese Wechselwirkungen eingehend untersucht. Dabei konnte eine Aktivierung der Gefässwandzellen festgestellt werden, die zur Herstellung der Botensubstanz CCL5 führte. Wir konnten zeigen, dass dieses CCL5 eine Ansammlung von Monozyten, einer Untergruppe weisser Blutzellen, in der Nähe von Tumorzellen bewirkt, welche die Entstehung von Metastasen fördern. Diese Beobachtungen helfen, das Verständnis für die Metastasenbildung zu erhöhen, und neue Krebstherapien zu ermöglichen, die diesen Prozess spezifisch hemmen.